SCOPOLAMINE-MORPHINE AS AN ADJUVANT IN THE ADMINISTRATION OF GENERAL ANÆSTHESIA.[1]

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THE purpose of this paper is to present a series of sixty-five general anæsthesia administrations, showing that the method used is one that merits recommendation and trial. This series included the following range of cases: Abdominal Hysterectomy, 8; Vaginal Hysterectomy, 6; Herniæ, 5; Plastic Operations, 8; Operations in the Tubes and Ovaries, 11; Uterine Fixations, 6; Curettements, 6; Hæmorrhoids, 3; Fistula in Ano, 2; Thyroidectomy, Craniectomy, Orchidectomy, Appendicectomy, Costectomy, Nephropexy, Tumor of Breast, Cyst of Neck, Pelvic Abscess, Exploratory Laparotomy, one each. In every instance the patient received a hypodermatic injection of scopolamine hydrobromate, grain 1/100, and morphine, grain 1/6, one half-hour before the administration of the general anæsthetic. The general anæsthesia was induced by means of the ethyl chloride-ether sequence administered through the Bennett inhaler.

The Bennett inhaler was used because an experience of five years with it has assured the writer of its practicability, and because he finds disadvantages in all other inhalers. In the recently described inhaler of Iglauer,[1] for example, the anæsthetist is unable to administer ether or gas at will, after once having started the administration of ether. Ethyl chloride is substituted for nitrous oxide gas, because it is practically as safe, induces quicker anæsthesia, causes no cyanosis or asphyctic symptoms, and obviates the necessity of transporting bulky steel cylinders of the compressed nitrous oxide gas. Herrenknecht,[2] in a most extensive monograph, confirms the above statements. Gaudiana[3] reaches the same conclusions, and shows that not one of the few instances of death laid at the door of ethyl chloride was solely due to the drug itself. Danill,[4] the instructor in anæsthetics at the Royal Infirmary, says of the ethyl chloride-ether sequence, "the method certainly has some advantages over the gas-ether sequence, and is a most excellent one. I have never had reason to complain of it, either from the point of view of safety or for any other reason. The advantages of the ethyl chloride-ether sequence are practical ones."

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[1] Read before the Medical Society of the City Hospital Alumni of St. Louis, May 18, 1905.

In order to make the Bennett inhaler suitable for the administration of ethyl chloride, a slight modification was necessary. A piece of small-caliber brass tubing (length 3 centimetres, lumen 1.5 millimetres) was inserted about one-half an inch distally to the air-valve. This brass tubing is placed obliquely, so as to throw the ethyl chloride spray towards the rubber bag of the inhaler, thus insuring against any of the fluid reaching the patient's face. By means of a three or four inch piece of rubber tubing, a connection is made between the ethyl chloride container and the inhaler, through the brass tube. These details show clearly in the appended illustrations. As the ethyl chloride container hangs suspended from the brass tube, the rubber tube kinks and effectively shuts off the escape of any ethyl chloride gas. By one movement the flask of ethyl chloride is turned spout end down, and the rubber tube straightened out, so that a measured quantity of the fluid runs into the rubber bag. There is no frosting or freezing, and consequently no more chance for the much talked of "refrigeration of the lung" than there is with any other anæsthetic. The method really simplifies the Bennett inhaler, in that it does away with the large and cumbersome gas-bag. In this very simplicity the modification seems to possess a decided advantage over the more complicated one recommended by Pedersen.[5]

At this day there is certainly no occasion for a statement

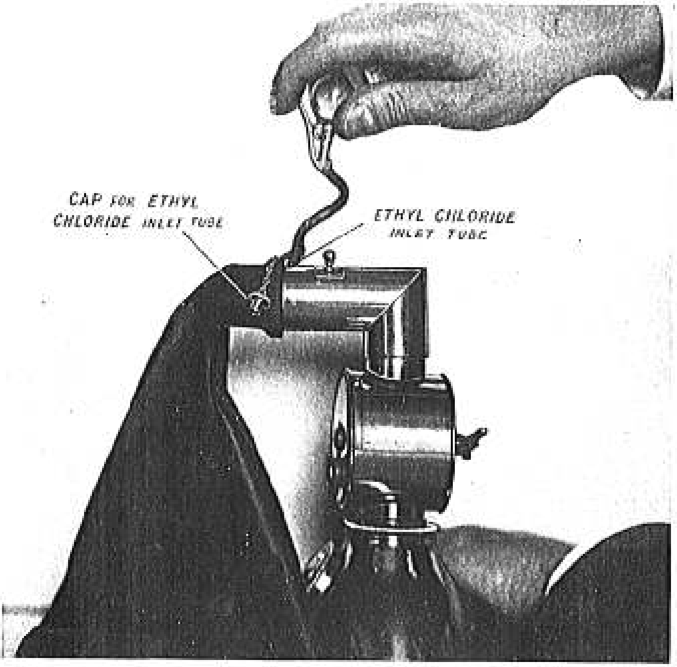

FIG. 1.—Bennett inhaler, modified for the use of the ethyl chloride-ether sequence.

of facts justifying the use of ether as a routine general anæsthetic. It has been shown repeatedly during the last few years that the formerly much dreaded "postoperative pneumonia" is by no means solely referable to ether. Aspiration of mucus and vomitus, exposure, and pulmonary embolism have been pretty clearly demonstrated to be the predisposing factors of postoperative pneumonias; and no particular anæsthetic, not even local anæsthesia, does away with the danger of exposure, of embolism, or of vomiting. Moreover, experimental proof is gradually accumulating to show that ether is not the only anæsthetic that has an injurious effect on the kidneys. Kemp[6] showed, as early as 1899, that "renal complications may follow *any* anæsthetic, . . . for there is no known anæsthetic administered in any effective quantity, whatever the method of administration, which does not affect the renal circulation." Moreover, M. Jaquet,[7] in a comprehensive investigation of the comparative merits of chloroform and ether, shows that chloroform causes a parenchymatous degeneration of all the organs, whereas, ether produces no histological lesions; and this fact has been confirmed in a lately published research of Offergeld.[8] The latter author even shows that the parenchymatous degeneration induced by chloroform may be the cause of death some time after the administration of the anæsthetic.

Unfortunately, the physiology of artificially induced anæsthesia is not positively known. The important conclusions worked out by Overton[9] are generally credited as being correct, and are already finding their place in standard works on physiology. For the clinician, the important aspect of Overton's work is not so much the establishment of the doctrine that anæsthetics act by going into solution in the lipoids (fat, cholesterin, and lecithin) of cells, as the other fact, that the injury wrought in these cells is directly proportional to the quantity of anæsthetic used. It is probably fair to assume that not one operator in a hundred concerns himself with the quantity of anæsthetic administered to his patient. Yet we read in one of the latest published works on physiology[10] that "cell death is caused by a prolonged anæsthesia." One of the ends to be aimed at in the administration of all the anæsthetics is to reduce the amount administered to a minimum. The ethyl chloride-ether sequence most positively aids us in the attainment of this end.

We are further aided, however, by the administration of scopolamine-morphine hypodermatically. Scopolamine is an alkaloid of hyoscyamus niger of the order of solanaceæ. Its sister alkaloids are hyoscine, daturine, duboisine, atropine, and hyoscyamine. Although much has been written concerning scopolamine (chiefly as a result of the investigations of psychiatrists and chemists), it still remains to be settled in just what particulars it differs from other alkaloids of the belladonna group. It is most closely related to hyoscine. Kunzel,[11] Steinbuechel,[12] Kochmann,[13] and others state that it is identical with hyoscine, whereas Ladenburg[14] claims to have shown that hyoscine and scopolamine are by no means identical. The best *résumé* of the physiological action of scopolamine is given by Steinbuechel.[12] He states:

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5. Sweat, mucus, and saliva secretion markedly diminished.
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7. Motor end-apparatus supplying the intestine paralyzed. Tone of the splanchnic increased.
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In 1900, Schneiderlin[15] published the first paper advocating the use of scopolamine as a substitute for general anæsthesia by inhalation. Scopolamine itself does not induce analgesia, but combined with morphine it induces a state of general anæsthesia sufficiently profound to permit the performance of any operation. The method of administration and dosage was more carefully worked out by Korff[16] and Blos;[17] as a result of Korff's work, in particular, the following dosage was adopted: Scopolamine, 0.0012, and morphine, 0.025. This was divided into three doses, administered hypodermatically, three, one, and one-half hours before the operation. Schneiderlin, Korff,[18] and Blos all reported excellent results.

Rational objections were gradually advanced against a method of inducing anæsthesia by means of fixed dosage, one author even going so far as to pronounce the method useless and dangerous.[19] In addition, three unfortunate deaths occurred during and following operations on patients to whom scopolamine and morphine had been administered. These deaths, although not wholly referable to the anæsthesia, nevertheless served to place scopolamine-morphine narcosis in discredit. There it remained until Carl Hartog[20] suggested that both the scopolamine and morphine be administered in much smaller doses than was recommended by previous authors, and that ether be relied upon to complete the anæsthesia. Hartog reported seventy-five cases, and spoke of his results in most glowing terms. It was my good fortune to observe most of the cases he reported, and to be able to confirm all his statements.

Through the kindness of Drs. Gellhorn, Ehrenfest, Witherspoon, Bartlett, and Mudd, I am able to report a series of sixty-five cases in which scopolamine hydrobromate, grain 1/100, and morphine, grain 1/6, were administered half an hour before inducing general anæsthesia with ethyl chloride-ether. In more than half the cases the anæsthetic was administered by Dr. W. E. Leighton. As a result of my experience with the method, I feel that I may say without reserve that I have never seen results even approximating those that were obtained by this method. Unstinted praise always carries with it the suspicion of a somewhat biased critique. Yet, so exceptionally smooth were these narcoses that they warrant one's carrying the burden of this suspicion until it is proved unfounded. Of these sixty-five cases only one vomited or retched while on the operating table. Seventy-seven per cent. of the cases *did not vomit at all.* One-third of the cases that did vomit, vomited only once, and then only from two drachms to one ounce of clear mucus. Nausea was never pronounced, except in two cases, and vomiting never occurred earlier than two hours after the operation. This last fact is of supreme importance, for in all cases where vomiting did occur, laryngeal sensibility was intact, and acted as a complete safeguard against tracheal aspiration, and the consequent danger of an aspiration pneumonia. There is no occasion for dilating upon either the discomforts or the dangers attendant upon post-anæsthetic vomiting. They are well known. I can find no record of a series of general anæsthesia administrations followed even by approximately so small a percentage of vomiting, and if the preliminary administration of scopolamine-morphine did nothing else than lessen the liability to vomit, its use should be highly recommended.

But it does more. First of all, it markedly lessens the quantity of anæsthetic necessary. About four ounces of ether per hour of operation are used when the drug is administered skilfully and carefully. In a personal communication to me, Dr. T. L. Bennett, of New York, tells me that he uses about four ounces of ether per sixty minutes of anæsthesia, and that for a two-hour operation he requires about six ounces. This averages three and a third ounces per hour. We used barely a fraction over two ounces an hour. It has already been pointed out how great a desideratum it is to administer a minimal quantity of ether.

After the administration of scopolamine-morphine the patients are in a peaceful state of mind, and go under the influence of the general anæsthetic without passing through the usual state of excitement. Salivation is almost invariably absent, thus adding another safeguard against aspiration pneumonia. After their return to bed the patients lie absolutely quiet and awaken without the slightest excitation. After remaining awake for a short period they usually doze off again, or at least remain quiet and peaceful. The first twenty-four hours following the operation is attended by much less pain and discomfort than in cases where the scopolamine is not administered. These advantages: lessened amount of anæsthetic necessary, absence of salivation, avoidance of the stage of excitement, marked reduction in the liability to vomit, and quiet and freedom from pain after operation have been confirmed by Tuffier,[21] of Paris, Israel[22] and Dork,[23] of Berlin, and by Robertson,[24] of our own country (Robertson used hyoscine instead of scopolamine).

There is no reasonable objection to the use of scopolamine hydrobromate and morphine in the doses recommended of 1/100 and 1/6 of a grain respectively. The recent experimental work of Crile[25] shows that morphine lessens the intensity of many of the afferent nerve impulses reaching the vasomotor centres, as the result of stimulation of the peripheral nerves, and thereby lessens the susceptibility to shock. Scopolamine exerts a distinct influence in raising blood-pressure, and thereby also aids in preventing shock. So, from the point of view of prophylaxis, the combination of the two drugs strongly recommends itself. Only he who has witnessed a series of ether administrations preceded by scopolamine-morphine injections can appreciate what a boon these drugs afford both to the patient and to the operator.*

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hydrobromate in tablets of 1/100 grains each. One of these tablets should be dissolved together with a one-sixth grain tablet of morphine and injected hypodermically thirty minutes before the administration of the general anæsthetic. Scopolamine may be used with advantage as an adjuvant to chloroform, as well as to ether.

BIBLIOGRAPHY.

[1] The Nitrous Oxide-Ether Sequence by Means of a New Inhaler. S. Iglauer. The Cincinnati Lancet-Clinic, March 18, 1905.
[2] Herrenknecht. Ueber Aethyl Chlorid und Aethyl Chlorid Narkose. Dr. William Herrenknecht. Leipzig, 1904.
[3] Ethyl Chloride Narcosis. Gaudiana. Riforma Médica, January 29, 1904
[4] Mixed Anæsthetics. G. W. Danill. Edinburgh Medical Journal, February, 1905.
[5] An Attachment to Bennett's Inhaler. Victor Pedersen. New York Medical Journal, December 24, 1904.
[6] Further Experimental Researches on the Effects of Different Anæsthetics on the Kidneys. R. C. Kemp. New York Medical Journal, November 18 and 25, December 2, 1899.
[7] Semaine Médicale, December 7, 1904.
[8] Experimenteller Beitrag zur toxischen Wirkung des Chloroforms auf die Nieren. Offergeld. Archiv für klin. Chir., Band lxxv, Heft 3.
[9] Studien über die Narkose. E. Overton. Jena, 1904.
[10] Vorlesungen über Physiologie, p. 26. M. v. Frey. Berlin, 1904.
[11] Kunzel. Handbuch der Toxicologie. Jena, 1899. Page 714.
[12] Steinbuechel. Schmerzverminderung und Narkose mit specieller Berücksichtigung der kombinirten Skopolamin-Morphium Anæsthesie. Leipzig, 1903. Franz Deuticke.
[13] Th. Kochmann. Ueber die therapeutischen Indicationen des Skopolamin-Hydrobromicum. Therapie der Gegenwart, May, 1903.
[14] Ladenburg, quoted by Roith. Bemerkungen zur Skopolamin Narkose. Monatsch. f. Geburtshulfe u. Gynäk. Band xviii, p. 627.
[15] Schneiderlin. Aerztliche Mittheilungen aus und für Baden, No. 10, 1900.
[16] Korff. Münch. med. Woch., No. 29, 1901, p. 1170, and No. 27, 1902, p. 1133.
[17] E. Blos. Beiträge zur klin. Chir., Band xxx, p. 565, 1902.
[18] Korff. Berl. klin. Woch., No. 33, 1904.
[19] Flatau. Münch. med. Woch., No. 28, 1904.
[20] C. Hartog. Die Aethernarkose, in Verbindung mit Morphium-Skopolamin Injectionen. Münch. med. Woch., No. 46, 1903.
[21] Gazette Médicale de Paris, No. 8, 1905.
[22] Deutsche med. Woch., No. 10, 1905.
[23] Deutsche med. Woch., No. 10, 1905.
[24] Medical Record, January 9, 1905.
[25] Blood-Pressure in Surgery. George W. Crile. J. B. Lippincott Company.